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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,843	PEROUTKA, STEPHEN J	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-33 are presented for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of headaches, it does not reasonably provide enablement for preventing headaches. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

A. Breath of the Claims: The complex of nature of the claim is greatly exacerbated by breath of the claim. The claims encompass prevention of headaches which have potentially many different causes (Current evidence indicates that experts continue to

debate the causes and even the name of tension headaches. Over the years, as different theories emerged about the origins of this type of headache, it was known by names such as muscle contraction headache, psychogenic headache, depressive headache, essential headache and ordinary headache. The exact cause or causes of tension headache are unknown. Until a few years ago, many researchers believed that the pain of tension headache stemmed from muscle contraction in the face, neck and scalp, perhaps as a result of heightened emotions, tension or stress. But many researchers have questioned this idea (see Mayclinic.com reference provided (U). With regard to migraine prevention, MayClinic.com (V) teach that migraine etiology is poorly understood, and there are many migraine triggers, including hormonal changes, foods, stress, sensory stimuli, changes in wake-sleep patterns, physical factors changes in the environment and medications. Similarly, regarding premenstrual headache (W), Mayclinic.com teach that not all women experience PMS such as a headache and state that the exact cause is unknown). Given these factors, there is a lack of predictability requiring undue experimentation for enabling the prevention of headaches.

B. Nature of the Invention: Claims 1-33 are drawn to a method of **preventing** a headache in a subject by administration of an effective amount of threo-3-(3,4-dihydroxyphenyl)serine (threo DOPS). The nature of the invention is extremely complex in that it encompasses the actual prevention of a headache that has many varied etiologies and in most cases the cause is poorly understood.

C. State of the Prior Art: While the state of the art is relatively high with regard to **treatment of a headache**, the state of the art with regard to **prevention** of such

disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** a headache, selected from a migraine, tension headache, premenstrual headache.

D. The Level of One of Ordinary Skill: The relative skill of those in the art is generally that of a physician or a physicians assistant.

E. Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the predictable **prevention** of a headache from the claimed etiologies makes practicing the claimed invention unpredictable in terms of prevention of a headache.

F. Guidance of the Specification: The guidance given in the specification supports the Examiners allegation of unpredictability. The specification at page 2 states that the administration of the "norepinephrine precursor" reduces the frequency, severity, intensity, and/or duration of a headache when administered prior to the headache's onset. An amount of the active agent that is effective in preventing the headache is any amount that reduces the frequency, severity, intensity, and/or duration of headaches in a subject being treated. The specific dose level and frequency of dosage may vary, and can depend upon a variety of factors, including the activity of the specific active agents, their metabolic stability and length of action, half- life, rate of excretion, mode and time of administration, and the age, body health, gender, diet, and severity, intensity, and frequency of the onset of the headache, of the particular condition of the subject

undergoing therapy. Given all of the above factors, required to effectively reduce the frequency or intensity of a headache makes the practice of prevention unpredictable.

G. Working Examples: All of the working examples provided by the specification are directed toward the treatment or reducing the intensity of a headache rather than prevention of a headache.

H. The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, and appropriate animal model system for one of the claimed compounds in addition to calculating the frequency, severity, intensity, and/or duration of headaches in a subject being treated, activity of the specific active agents, their metabolic stability and length of action, half- life, rate of excretion, mode and time of administration, and the age, body health, gender, diet, and severity, intensity, and frequency of the onset of the headache, and test the combination in the model system to determine whether or not the combination is effective for **prevention** of migraine headaches, premenstrual headaches, tension type headaches or headaches in general. If unsuccessful, which is likely, given the lack of significant guidance from the specification or prior art with regard to prevention of migraines, tension headaches or PMS headaches with any compound, one of skill in the art would have to then either envision a modification of the norepinephrine precursor, composition dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is

likely given the lack of significant guidance from the specification of prior art regarding prevention of headaches, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent a headache, migraine headache, tension headache or premenstrual headache in a subject by administration of one of the claimed norepinephrine precursor compositions.

Therefore, a method of **preventing** a headache by one of the above causes comprising administering threo DOPS or a norepinephrine precursor is not considered to be enabled by the instant specification.

Claims 18-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Claims 18-26 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following precedent is believed relevant to the instant case.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed.Cir.1997), *cert. denied,* 523 U.S. 1089, 118 S.Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly,* 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description"

Requirement ("Guidelines"), 66 Fed.Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia,* "functional characteristics *when coupled with a known or disclosed correlation between function and structure ....*" *Enzo Biochem, Inc. v. Gen-Probe Inc.,* 296 F.3d, 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed.Reg. at 1106 (emphasis added)). Moreover, although Eli Lilly and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp.2d 216, 225 (W.D.N.Y. 2003).

Applying the reasoning of the above-cited case law to the facts at hand, the instant specification fails to provide an adequate written description for identifying a suitable norepinephrine precursor, other than the claimed threo DOPS in claims 1-17 and 27-33. The specification states that "a norepinephrine precursor comprises any compound which is converted into the norepinephine neurotransmitter. These include, e.g., a substrate of the enzyme dopa decarboxylase that can be converted to norepinephrine, such as **threo-3-(3,4-dihydroxyphenyl)serine,** or a substrate of the enzyme **dopamine beta-hydroxylase** that can be converted to norepinephrine, such as **dopamine**." (see page 3 of the specification).

No other detailed, relevant identifying characteristics are specified which would adequately describe suitable norepinephrine precursors. Also see Genentech, Inc. v. Novo Nordisk, 108 F.3d 1361, 1366, 42 U.S.P.Q.2d (BNA) 1001, 1005 (Fed. Cir. 1997)

(clarifying that the patent monopoly is given in exchange for enabling disclosure, "not for vague intimations of general ideas that may or may not be workable"); see also Brenner v. Manson, 383 U.S. 519, 536, 148 U.S.P.Q. (BNA) 689, 696 (1966) ("[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Claims 10-16 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals, such as N-methyl-3-(3,4-dihydroxyphenyl)serine alkyl esters, such as N-methyl-D,L-threo-3-(3,4-dihydroxyphenyl)serine and N-methyl-L-threo-3-(3,4-dihydroxyphenyl)serine, lower alkyl esters, methyl esters, ethyl esters, n-propyl esters and isopropyl esters as described in U.S. Pat. No. 5,288,898 which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 10-17 aredirected to encompass derivatives which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these undisclosed derivatives, meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claims 3, 12 and 18 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that by serotonin precursors, it means those serotonin precursors as disclosed in U.S. Pat. 5,939,076 which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 3, 12 and 18 are directed to precursors of serotinin, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these unnamed precursors meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

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Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi U.S. Patent No. 5,616,618 A.

Takagi teaches administration of threo DOPS to treat headaches and migraine (see abstract). It further teaches that L-threo DOPS is the preferred form for treatment of pain (column 2, lines 29-32). The specific exclusion o f patients with Parkinson's disease is noted in the instant claims. While Takagi mentions that the agent has been employed in the treatment of Parkinson's disease to improve "freezing gait" (column 2, lines 32-34), the treatment of headache pain is not particularly directed to Parkinson's patients.

Addressing instant claim 4, drawn to the method of preventing headaches wherein benserazide is not administered, Takagi teaches administration of threo DOPS with and without benserazide (see examples).

Regarding the exclusion of a serotonin precursor, there do not seem to be any instances where threo DOPS is administered with a serotonin precursor. Addressing instant claim 33, drawn to administration of threo DOPS with a decarboxylase inhibitor,

Takagi teaches administration of threo DOPS with at lease one decarboxylase inhibitor selected from benserazide and carbidopa (see claim 2 of the patent).

Takagi does not teach the relief of premenstrual headaches or tension type headaches, however it teaches that threo DOPS is an analgesic composition useful for acute and chronic pain (column 1, lines 34-37). The prior art showed relief of migraines and headaches and further disclose that threo DOPS is an analgesic useful for acute and chronic pain. Therefore, it would have been obvious to one of ordinary skill in the art to employ the threo DOPS for the predictable result of treatment of tension headaches and premenstrual headaches because it is taught in Takagi for the treatment of acute and chronic pain in addition to treatment of headaches and migraine headaches.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1614

October 1, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614